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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/988,115	11/16/2001	James M. Robl	50195/008003	8075

21559 7590 04/20/2005

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/988,115	ROBL ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,10-14,21,23-26,28,29 and 49-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10-14,21,23-26,28,29 and 49-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/9/04, 1/31/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's arguments filed January 31, 2005 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-5, 10-14, 21, 23-26, 28, 29 and 49-65 are examined in this office action.

The rejection made in the previous office action under 35 U.S.C. 103(a) is withdrawn in view of applicant's amendments to the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 10-14, 21, 23-26, 28, 29 and 49-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic bovine whose somatic and germ cells comprise xenogenous artificial chromosomes comprising heavy and light chain that undergo rearrangement in B-cells to produce functional xenogenous antibodies in response to exposure to antigen or antigens, B-cells from the ungulate comprising a rearranged xenogenous Ig locus and produces xenogenous antibody and methods of producing antibodies comprising exposing the ungulate to antigen or antigens and recovering the antibodies, does not reasonably provide enablement for the breadth of the claims as presently written. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are to a transgenic ungulate comprising one or more artificial chromosomes comprising one or more immunoglobulin loci that undergo rearrangement and express a xenogenous immunoglobulin molecule comprising nucleic acids encoding all or part of a xenogenous immunoglobulin (Ig) gene which undergoes rearrangement and

expresses more than one xenogenous Ig molecule, an ungulate somatic cell comprising nucleic acids encoding all or part of a xenogenous Ig gene which undergoes rearrangement and expresses more than one xenogenous Ig molecules in B cells, methods of producing antibodies comprising administering one or more antigens to the ungulate wherein the gene undergoes rearrangement resulting in the production of antibodies specific for said antigens and recovering the antibodies from the ungulate, and methods of producing antibodies comprising recovering antibodies from the ungulate where an artificial chromosome comprising immunoglobulin loci, the loci undergo rearrangement resulting in the production of antibodies.

The claims are not fully enabled because the specification does not provide evidence or guidance that an ungulate can produce xenogeneic antibodies and in particular does not provide evidence or guidance for the production of human antibodies. Cows, sheep and pigs have a relatively small number of functional germ line V-genes, which imposes constraints in the generation of antibody diversity as compared with animals such as humans and mice that possess a large pool of divergent VDJ genes that cause significant diversity. In sheep and bovines, antibody diversity takes place in the Ileal Payer's patches, where somatic hypermutations take place during B cell development (see Parng, pages 5478 and 5479). Sheep and bovine B cells develop without the influence of maternal antibodies, and selective forces operating during B cells development are different from those observed in mice and humans where maternal antibodies influence the developing B cell repertoire. (see Kaushik, pages 347 and 348, col. 1). Thus, it is not clear that a human or other nonungulate antibody locus would undergo rearrangement and develop even immature B-cells under the mechanism found in the Ileal patch, or that that B-cells maturation would occur responsive to a particular antigen. In humans, B-cells are made in the bone marrow and travel to the lymph nodes for maturation into particular antibody secreting cells. The B-cells reaching the

lymph node are committed to a certain antibody lineage. Since the B-cell maturation process is so very different from that found in humans, for example in claim 2, it is very likely that antibody diversity would not be found or that no antibodies would be produced.

Applicant's arguments and post-filing reference (Kuroiwa et al.) are persuasive for the scope limitation given. In particular the limitation has been given to provide that the bovine comprises those elements essential to the disclosed purpose, the production of xenogenous antibodies. In order to accomplish this, both Ig heavy and light chains would bee needed, and rearrangement via the variable region would be necessary to produce a repertoire of antibodies in response to antigen or antigens. Further rearrangement and antibody production does not occur in fibroblasts.

The rejection based upon the production of antibodies in bovines rather than all ungulates is maintained for reasons presented in the previous office action.

The claims are free of the prior art. At the time of filing, the prior art did not teach nor suggest a transgenic ungulate comprising one or more artificial chromosomes comprising one or more immunoglobulin loci that undergo rearrangement and express a xenogenous immunoglobulin molecule comprising nucleic acids encoding all or part of a xenogenous immunoglobulin (Ig) gene which undergoes rearrangement and expresses more than one xenogenous Ig molecule, an ungulate somatic cell comprising nucleic acids encoding all or part of a xenogenous Ig gene which undergoes rearrangement and expresses more than one xenogenous Ig molecules in B cells, methods of producing antibodies comprising administering one or more antigens to the ungulate wherein the gene undergoes rearrangement resulting in the production of antibodies specific for said antigens and recovering the antibodies from the ungulate, and methods of producing antibodies comprising recovering antibodies from the ungulate where an artificial chromosome

comprising immunoglobulin loci, the loci undergo rearrangement resulting in the production of antibodies.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

April 15, 2005